

REMARKS

Upon entry of the present amendment, claims 1-3, 5-8,10-11, and 13-26 will remain pending in the above identified application, with claims 21-26 standing ready for further action on the merits, and claims 1-3,5-8, 10-11 and 13-20 standing withdrawn from further consideration on the merits based on an earlier restriction requirement of the Examiner.

The amendments made herein to the claims do not incorporate new matter into the application as originally filed. For example, claim 21, has simply been amended to change the phrase "the oil droplets" to "an oil droplet", in order to over come the Examiner's concerns under 35 USC § 112, second paragraph.

Because the instant amendment to claim 21 does not incorporate new matter into the application as originally filed, and at the same time serves to remove issues outstanding, while also not requiring any further search or new consideration by the Examiner, it follows that entry of the instant amendment is appropriate at present.

Enclosed 37 CFR § 1.132 Declaration

Enclosed herewith is a 37 CFR § 1.132 declaration of Dr. Nomura, which is pertinent to a consideration of the patentability of the instant invention as claimed. The Examiner is respectfully requested to review Dr. Nomura's enclosed Declaration at this time,

as it is material to a consideration of the patentability of the pending claims under consideration at present. The enclosed Declaration is the second 37 CFR § 1.132 declaration of Dr. Nomura that has been filed in the matter of this case.

Claim Rejections - 35 USC § 112, Second Paragraph

Claims 21-25 have been rejected under the provisions of 35 USC § 112, second paragraph. Reconsideration and withdraw of this rejection is respectfully requested based on the following considerations.

First, claim 21 does not recite the language "obtain by" as asserted by the Examiner in paragraph "9." of the office action. Instead, claim 21 recites the language "obtained by" which is submitted to be entirely appropriate under the provisions of 35 USC 112, second paragraph.

Second, claim 21 has been amended herein to recite "an oil droplet" instead of "the oil droplets", so that proper antecedent basis is provided for the same.

Accordingly, because each of pending claims 21-26 under consideration at present, particularly and distinctly set forth the inventive discovery that the Applicants regard as their own, it follows that the pending claims under consideration fully comply with the provisions of 35 USC § 112, second paragraph. Any contentions of the USPTO to the contrary must be reconsidered.

Claim Rejections Under 35 USC § 102(b)/102(e)

Claims 21 and 23-26 have been rejected under the provisions of 35 USC § 102(b) as anticipated by Yamamura et al. (US 4,543,253), or Cantrell (US 4,877,611), or Yarkoni et al. (*Infection and Immunity*, 28(3):881-886 (1980)). Claims 21 and 23-26 have also been rejected under the provisions of 35 USC § 102(e) as anticipated by Van Nest et al. (US 6,451,325 B1).¹ Reconsideration and withdraw of these rejections are respectfully requested based on the following considerations.

Oil-in-Water Emulsions of the Present Invention

The oil-in-water emulsion according to amended claim 21 is characterized in that the emulsion, has the properties:

- 1) that the emulsion is negative for agglutination reaction with lectin;
- 2) that a BCG-CWS is encapsulated in an oil to form oil droplets; and
- 3) that the particle diameter of the oil droplets is 100 μ m or less.

These properties are provided in emulsions by means of the process defined in claim 24, steps (a), (b) and (c), especially the

¹ In the outstanding office action, the Examiner indicates that the rejection over Van Nest, et al. (US 6,451,325 B1) is being maintained under the provisions of 35 USC § 102(b); however, this is submitted to be incorrect, as the Van Nest et al. US 6,451,325 B1 patent issued on September 17, 2002, which is after the March 22, 2001 filing date of the present application.

use of an organic solvent in the preparation of a mixture of BCG-CWS and an oil.

When a BCG-CWS is dispersed without any organic solvent, then a particle diameter of the BCG-CWS should exceed 100 μm in size.

Distinctions Over the Cited Art

It is submitted that the Examiner misunderstands the invention described in Yamamura et al. In Yamamura et al., ethanol or acetone described as an organic solvent is used merely to wash the CWS, which has been prepared from the culture (see column 9). Yamamura et al. neither describes nor suggests any preparation method wherein an organic solvent is used in the preparation of a mixture of BCG-CWS and an oil.

Accordingly, Yamamura et al. describes no emulsion comprising a BCG-CWS having a particle diameter of about 100 μm or less. This is because the enclosed 37 CFR § 1.132 Declaration of Dr. Nomura demonstrates that the Yamamura et al. method, without an organic solvent, provides a mixture of particles having a large particle size.

Therefore, the invention of the present application is novel over the disclosure of Yamamura et al. Any contentions of the USPTO to the contrary must be reconsidered.

Notably, the remaining cited references also neither describe nor suggest any preparation method wherein an organic solvent is used in the preparation of a mixture of BCG-CWS and an oil.

The Examiner mentions in the Office Action that the previously submitted 37 CFR § 1.132 Declaration of Dr. Nomura does not compare the oil-in-water emulsion of the prior art with the instantly claimed oil-in-water emulsion. Thus, submitted herewith is a second 37 CFR § 1.132 Declaration of Dr. Nomura.

Dr. Nomura's second Declaration demonstrates that the properties of an oil-in-water emulsion, prepared using an organic solvent are different from those of an emulsion prepared without using an organic solvent. Specifically, the oil-in-water emulsion, which is prepared not using an organic solvent, includes BCG-CWS, which is not covered by oil (that is, existing outside of an oil-droplet).

It has been known that BCG-CWS shows no inhibitory effect on tumor metastasis in the absence of an oil (see "Reference 2.3" and "Table 9" in the instant specification at pages 38-39).

The enclosed article of Berton Zbar et al., "Journal of the National Cancer Institute", vol. 48, No. 3, pp. 831-835, March 1972 has also reported that BCG cell wall was not effective as an anti-tumor agent even if it was administered with oil, when it was not included in an oil droplet (see attached copy). This means that a pharmaceutical product comprising BCG-CWS, which is not prepared

using an organic solvent, should not be effective in drug efficacy, and such a product would contain an effective ingredient in a poor amount.

Although, needless to say, pharmaceutical products require a high quality, and in biopharmaceuticals including emulsions (such as that of the present invention) it is often more difficult to maintain a high quality than in other chemical products.

The formulation of "Reference 2.1" in the present application (see page 37), which is prepared without using an organic solvent, also shows an inhibitory effect on tumor metastasis (see Table 9 at page 38). Accordingly, even if one argues that there is not a significant difference in drug efficacy between the emulsion of the present invention and the prior art, nonetheless, a pharmaceutical product having a purity of 95% and one having a purity of 99.9% are not equivalent drug products, even if there is not a significant difference in drug efficacy between them. Since obviously, pharmaceutical products having a purity of only 95% can not be used as drug products.

As shown in the enclosed 37 CFR § 1.132 Declaration of Dr. Nomura, an organic solvent is necessary to prepare an emulsion from BCG-CWS and an oil for use as a drug product, which retains the drug efficacy of the effective ingredient.

CONCLUSION

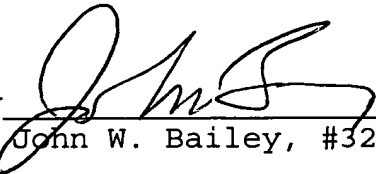
Based on the amendments and remarks presented herein, as well as the submission of Dr. Nomura's enclosed second declaration, it is submitted that each of the pending claims under consideration is allowable at present. Accordingly, the Examiner is respectfully requested to issue a notice of allowance at present indicating the allowability of each of pending claims 21-26.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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By 
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Attachment(s) :

37 CFR § 1.132 Declaration of Dr. Nomura (Second Declaration of Mr. Nomura); and

Berton Zbar, et al. "Tumor Suppression by Cell Walls of *Mycobacterium bovis* Attached to Oil Droplets", J Nat Cancer Inst 48: 831-835, 1972.

(Rev. 02/12/2004)